WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/051025

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15 and 16 (as regards industrial applicability)

because:

☒ the said international application, or the said claims Nos. 15 and 16 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5, 9-16
	No:	Claims	6-8
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

The present **claims 15** and **16** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
Consequently, no opinion will be formulated with respect to industrial applicability of the subject-matter of these claims.

[For the assessment of the aforesaid claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a (known) *compound for* first *use in medical treatment* and the *use* of such a compound *for the manufacture of a medicament* for a new medical treatment.]

Re Item V.

The following documents (D) are considered to be relevant:

D1: ..... WO-A-97/35854 (2 October 1997);
D2: ..... WO-A-2004/019944 (***11 March 2004***);
D3: ..... WO-A-2004/019945 (***11 March 2004***);

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-16** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The compounds of present **claim 1** are novel over the prior art **D1** on account of

(i) the ***oxy*** *group* attached to either ***position 2*** or ***3*** of the phenanthridine ring (cf., the definitions of the present substituent groups R4 and R5 according to which either R4 represents ***-O-R41*** (and R5 is hydrogen or 1-4C-alkyl) or R5 represents ***-O-R51*** (and R4 is hydrogen or 1-4C-alkyl)), and

(ii) the definition of the present substituent group ***R7***: if R7 represents a 1-4C-alkyl group *it has to be substituted with a group R8* (cf., the *unsubstituted* 1-4C-alkyl group according to claim 1 of **D1**).

They are furthermore novel over **D2** and **D3** (both published on ***11 March 2004***) on account of the present substituent group ***R7***:
The 6-phenyl group of the present 1,2,3,4,4a,10b-hexahydro-phenanthridin-(2- or 3-)-ol derivatives has to be substituted with a *-N(R61)-C(=O)-**R7*** substituent (cf., the general formula I) wherein
R7 represent a ***heterocyclic*** *ring* (cf., the present groups *Het1* and/or *Har1*), a ***3-7C-cycloalkyl*** *group*, or a *1-4C-alkyl group* substituted by ***R8*** (where ***R8*** cannot be *hydrogen*), whereas
the 6-phenyl group of the 1,2,3,4,4a,10b-hexahydro-phenanthridin-(2- / 3-)-ol derivatives of **D2** and **D3** may only be substituted with an (*unsubstituted*)
-NH-C(=O)-1-4C-alkyl group (cf., the definitions of the substituent group R6 according to claim 1 of **D2** and **D3**).

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 6-8** does not appear to involve an inventive step (Rule 65(1)(2) PCT):

2.1. It would appear that the present **claims 1-5** and **9-16** are **fully entitled** to the presently claimed **first** priority date of ***09.03.2004***.

Accordingly, the documents **D2** and **D3** - which are both published on ***11.03.2004*** - may **not** be taken into account for the assessment of the question of inventive step.

The compounds of the present **claim 1 differ** from the compounds of **D1** in that they have

(i) an **oxy** *group* attached to either ***position 2*** or ***3*** of the phenanthridine ring (cf., the definitions of the present substituent groups R4 and R5 according to which either R4 represents ***-O-R41*** (and R5 is hydrogen or 1-4C-alkyl) or R5 represents ***-O-R51*** (and R4 is hydrogen or 1-4C-alkyl)) and

(ii) a ***Het1***-C(=O)-N(R61)-, a ***Har1***-C(=O)-N(R61)-, a ***3-7C-cycloalkyl***-C(=O)-N(R61)-, or a 1-4C-alkyl(*substituted with* ***R8***)-C(=O)-N(R61)- group attached to the 6-phenyl group.

In the light of **D1** the **problem** to be solved by the present application resides in the

provision of further 6-phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridine derivatives useful as *PDE4 inhibitors*.

The said problem has been **solved** by the compounds of the present **claim 1** (cf., the activity data (*PDE4 inhibition*) of table A on page 60 of the present description).

Given the structural differences between the present phenanthridine compounds and the phenanthridine compounds of **D1** (cf., the item (i) and (ii) above), it is considered that the present solution (i.e., the subject-matter of the present compound **claims 1-5**) has to be regarded as being non-obvious in the sense of Article 33(3) PCT.

It is therefore considered that the subject-matter of the present **claims 1-5** and **9-16** involves an inventive step as set forth in the Article 33(3) PCT

2.2. It would furthermore appear that the present **claims 6** and **8** (see, the last compounds) are **only entitled** to the **second** priority date of ***27.01.2005***, and the present **claim 7** (see, in particular, the definition of the radical R7C(O)N(R61)-) only to the present filing date of ***08.03.2005***.

Accordingly, the documents **D2** and **D3** - which are both published on ***11.03.2004*** - are considered to represent state of the art in the sense of Article 33(3) PCT.

2.2.1. The compounds of the present **claims 6** and **7 differ** from the compounds of the prior art **D2** essentially only in that they have a ***Het1***-C(=O)-N(R61)-, a ***Har1***-C(=O)-N(R61)-, a ***3-7C-cycloalkyl***-C(=O)-N(R61)-, or a 1-4C-alkyl(*substituted with **R8***)-C(=O)-

N(R61)- group attached to the 6-phenyl group (cf., the (*unsubstituted*) *-NH-C(=O)-1-4C-alkyl group* according to claim 1 of **D2**; and the *acetamide* of the example 45 of **D2**).

In the light of **D2** the **problem** to be solved by the compounds of the present **claims 6** and **7** resides in the provision of further 6-phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** derivatives useful as *PDE4 inhibitors*.

The said problem has been **solved** by the compounds of the present **claims 6** and **7** (cf., the activity data (*PDE4 inhibition*) of table A on page 60 of the present description).

Given the teaching of **D2**, it is considered that this solution does not appear to involve an inventive step for the following reasons:

1. It is known from **D2** that 6-[(*1-4C-alkyl*carbonylamino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** derivatives possess *PDE4 inhibitory* activity.

2. It is further known from **D2** (cf., claim 1 therein) that in *PDE4 inhibitors* of the 6-phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** type *cycloalkyl* and *alkoxyalkyl* groups may be regarded as structural equivalents to *alkyl* groups (see, for example, the definitions of
(i) the substituent groups R1, R2, R6 and R7 which comprise *alk*oxy and *cycloalk*oxy groups,
(ii) the substituent group R61 which comprises *alkyl* and *cycloalkyl* groups, and
(iii) the substituent group R4 which comprises *alkyl* and *alkoxyalkyl* groups).

3. The person skilled in the art would thus have expected that the accordingly modified 6-(*1-4C-alkyl*carbonylamino)phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives of **D2** (cf., e.g., the 6-[4-(*acetyl*amino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivative of the example 45 of **D2** and (i) the 6-[4-(***cyclopropyl***-carbonylamino)phenyl]- and the 6-[4-(***methoxy****acetyl*amino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives of the present examples 7 and 9) would also

possess (some) *PDE4 inhibitory* activity.

It is therefore considered that - in the absence of any ***unexpected / surprising effect*** - the compounds of the present **claims 6** and **7** have to be regarded to be **obvious** in the light of the teaching of **D2**.

2.2.2. The **last** compound of the present **claim 8 differs** from the corresponding compound according to claim 1 of the prior art **D3** essentially only in that it is ***Cyclo****propane*carboxylic acid amide rather than e.g. an *isopropyl*carboxylic acid amide.

In the light of **D3** the **problem** to be solved by the **last** compound of the present **claim 8** resides in the provision of a <u>further</u> 6-phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridin-***3-ol*** derivative useful as *PDE4 inhibitors*.

The said problem appears to be **solved** by the compound of the present example 40.

Given the teaching of **D3**, it is considered that this solution does not appear to involve an inventive step for the following reasons:

As it is known from **D3** (cf., claim 1 therein) that in *PDE4 inhibitors* of the 6-phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridin-***3-ol*** type *cycloalkyl* and *alkoxyalkyl* groups may be regarded as structural equivalents to *alkyl* groups (see, the definitions of
(i) the substituent groups R1, R2, R6 and R7 (*alk*oxy and *cycloalk*oxy),
(ii) the substituent group R61 (*alkyl* and *cycloalkyl*), and
(iii) the substituent group R4 (*alkyl* and *alkoxyalkyl*),
it is considered that the person skilled in the art would have expected that the accordingly

modified 6-(*1-4C-alkyl*carbonylamino)phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridin-*3-ol* derivative of **D3** (see, the ***Cyclo****propane*carboxylic acid amide of the present example 40) would also possess (some) *PDE4 inhibitory* activity.

It is therefore considered that - in the absence of any ***unexpected / surprising effect*** - the **last** compound of the present **claim 8** has to be regarded to be **obvious** in the light of the teaching of **D3**.

2.2.3. It is furthermore noted that the subject-matter of the present dependent **claims 6** and **7** appears to lack **unity** within the meaning of Rule 13 PCT:

The compounds of the present **claims 6** and **7 differ** from the 6-phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** derivatives of their closest prior art **D2** essentially only in that they have
(i) a ***heterocyclic*** *ring* (cf., the present groups *Het1* and/or *Har1*),
(ii) a ***3-7C-cycloalkyl*** *group*, or
(iii) a ***R8*** substituted *1-4C-alkyl group* (wherein ***R8*** cannot be *hydrogen*)

attached to the 6-phenyl group (cf., the (*unsubstituted*) *-NH-C(=O)-1-4C-alkyl group* according to claim 1 of **D2**; and the *acetamide* of the example 45 of **D2**).

The only structural feature discernible, which is shared by **all** of the compounds of the present dependent **claims 6** and **7** is the

6-[(*carbonylamino*)phenyl]-8,9-*dimethoxy*-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol*

moiety.

The document **D2**, however, already describes a 6-[(*carbonylamino*)phenyl]-8,9-*dimethoxy*-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* compound (cf., the compound of the example 45) *for the same use* (*PDE4 inhibition*) as the compounds according to claims 6 and 7 of the present application.

As the only structural feature which is common to all of the present compounds (i.e. the 6-[(*carbonylamino*)phenyl]-8,9-*dimethoxy*-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* moiety) is not novel (cf., **D2**), it cannot represent the "special technical feature" within the meaning of Rule 13.2 PCT.

The present application thus relates to different solutions to the given technical problem (i.e., the provision of <u>further</u> *PDE4 inhibitors*) which are not linked by a single general inventive concept as set forth in Rule 13.1 PCT.

Having regard to e.g. example 45 of **D2** it would appear that there are **five** separate inventions / groups of inventions which are not so linked as to form a single general inventive concept:

(i) the compounds of the present **claims 6** and **7** wherein the group **R7** represents a ***heterocyclic*** *ring* (cf., the present groups *Het1* and/or *Har1*) - which **differ** from the compounds of **D2** (see, e.g., the example 45) in that they are 6-[(***heterocyclyl***carbonylamino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives rather than 6-[(1-4C-*alkyl*carbonylamino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives;

(ii) the compounds of the present **claims 6** and **7** wherein the group **R7** represents ***cyclopropyl*** - which **differ** from the compounds of **D2** (see, e.g., the example 45) in that they are 6-[(***cyclopropyl***carbonylamino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives rather than 6-[(1-4C-*alkyl*carbonyl-amino)phenyl]-

1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives;

(iii) the compounds of the present **claims 6** and **7** wherein the group **R7** represents *1-4C-alkyl* substituted with ***methoxy*** - which **differ** from the compounds of **D2** (see, e.g., the example 45) in that they are 6-[(***methoxy****(1-4C-alkyl)*carbonyl-amino)-phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives rather than 6-[(1-4C-*alkyl*carbonylamino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives;

(iv) the compounds of the present **claims 6** and **7** wherein the group **R7** represents *1-4C-alkyl* substituted with ***carbamoyl*** or ***dimethylaminocarbonyl*** - which **differ** from the compounds of **D2** (see, e.g., the example 45) in that they are 6-[(***carbamoyl****(1-4C-alkyl)*carbonylamino)-phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives rather than 6-[(1-4C-*alkyl*carbonylamino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives; and

(v) the compounds of the present **claims 6** and **7** wherein the group **R7** represents *1-4C-alkyl* substituted with ***-N(R81)R82*** - which **differ** from the compounds of **D2** (see, e.g., the example 45) in that they are 6-[(***amino****(1-4C-alkyl)*carbonyl-amino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives rather than 6-[(1-4C-*alkyl*carbonylamino)phenyl]-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-14** concerns chemical compounds, pharmaceutical compositions and the use of chemical compounds for the production of pharmaceutical compositions and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.